4 Improving pharmacovigilance

Chapter 4.1

Intensive monitoring of new drugs based on first delivery signals from pharmacists: a pilot study

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Abstract

Intensive monitoring can be a valuable tool in the early detection of adverse drug reactions, especially of new drugs. Aim of this pilot study was to investigate the practical possibilities of a system of intensive monitoring, using the pharmacy computer system to detect the first dispensing of a new drug.

Methods
Eight pharmacists were asked to monitor, using their computer system, when a general practitioner prescribed the target drug (rofecoxib). The pharmacists were also requested to provide the researchers at Lareb with an overview of the patient's medication history. Subsequently, the pharmacist sent the prescribing physician an envelope containing information about the project and a reporting form (all provided by Lareb), which the GP was requested to return to Lareb after the next visit of the patient. The items on the questionnaire concerned characteristics of the patient (anonymous), indication, dose and information about possible adverse drug reactions.

Results
During a four-week period the participating pharmacists signalled 44 first prescriptions of rofecoxib. For each of these signals the pharmacist provided Lareb with the medication history of the patient involved. Of the prescribing GPs who had been sent the report form 70,5% (n=31) returned the form. Twenty-one of the 31 forms were returned within four weeks. The medication histories showed that in 43 of the 44 cases the dispensing of the target drug was indeed the first delivery.
The participating pharmacists and GPs were also sent an evaluation form. All pharmacists returned their evaluations, indicating an overall motivation to participate in the proposed system. In total seven GPs returned their evaluation forms, three of whom had not reported adverse drug events to the national spontaneous reporting centre before.

Conclusion
Although the number of participants in this trial was small, we conclude that pharmacists and prescribing physicians are able and willing to contribute to an intensive monitoring system for new drugs.

4.1.1 Introduction

Once a drug has been approved for marketing, the use of the drug attains the character of research in daily practice.(1) The facts about the drug that are known at that stage are limited in that they are based on research of a restricted population, a sample, moreover, that differs from the general population that will be using the new drug. This emphasises the importance of close and careful monitoring of the drug immediately following its introduction and the need for any unwanted adverse events to be detected at the earliest possible stage. Pharmacovigilance is the science dedicated to this monitoring process. Drugs monitoring is predominantly based on reports of suspected adverse drug reactions from medical doctors (GPs) and pharmacists, the so-called spontaneous reporting system (SRS), for which purpose most countries have established national reporting centres.(2) The number of reports submitted during the initial period following the introduction of a new drug is reflected by a distinctive curve, first described by Weber and later adapted by others(3,4,5). This curve is characterised by a slow rise, reaching its peak near the end of the second year, followed by a slow, gradual drop to a lower, more or less constant decreasing value. This implies that in the early stages after a drug has been released little information is available from clinical practice. However, it is essential that any negative effects of new drugs are identified as quickly as possible in order to prevent harm to patients. This has become all the more crucial since increasingly new drugs are developed that have a powerful impact on the human physiology. Moreover, the registration procedure for drugs targeting illnesses for which no adequate therapy is available has recently been shortened.

In this chapter we describe a pilot study in which we tested a detection method specifically aimed at this first stage after the introduction of a drug that will allow us to obtain an expedited first impression of possible unknown adverse events. The method involves Intensive Monitoring, and makes use of the data pharmacists collect regarding the first prescription and dispensing of a newly approved drug.

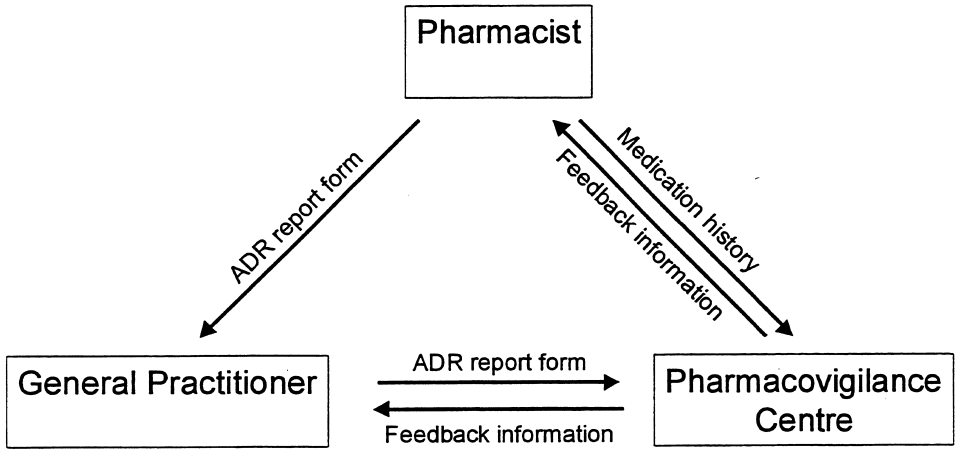
Intensive Monitoring is a prospective observation-based cohort study investigating a specifically selected (new) drug.(6,7) New Zealand has the most comprehensive set of data on the practical implementation of the method because in this country an Intensive Medicines Monitoring Programme (IMMP) supplementing the spontaneous reporting system has been operational since 1977. The IMMP is a constituent component of the Dunedin-based Centre for Adverse Reaction Monitoring (CARM), which independent organisation runs the SRS on behalf of the New-Zealand Department of Public Health.(6,8) The IMMS makes use of a permanent cohort of approximately 10,000 drug users. The prescription data are derived from the prescriptions dispensing pharmacists and hospital pharmacists receive and report. Within two months the IMMS sends the prescriber a questionnaire.

In the United Kingdom another form of Intensive Monitoring, the so-called Prescription Event Monitoring (PEM) has been in existence since 1980.(9,10) This system makes use of the prescriptions clinicians submit to the Prescription Pricing Authority. This allows the Drug Safety Research Unit (DSRU) to collect cohorts of 20 to 30,000 prescriptions of the drugs under investigation and it sends the prescribing physicians questionnaires, so-called green forms, three to twelve months after the date of the first prescription. The Southampton-based DSRU is an independent organisation founded to complement the SRS.(11)
Both in New Zealand and in the United Kingdom there is an interval of several months between the moment the monitoring of a drug is has started until the moment the first data of the Intensive Monitoring become available. We have tried to devise a fast method that would cause the pharmacist, the prescribing clinician and the national reporting system as little inconvenience as possible. The aim of the present pilot study was to explore the possibility to expedite this process by making use of the first delivery signals from pharmacies allowing the moment when data on newly released drugs become available to be brought forward.

4.1.2 Method

For the duration of one month in the spring of 2001 seven pharmacists, of whom one was associated with two separate pharmacies, were requested to signal when a patient was prescribed rofecoxib, the drug selected for this pilot study, for the first time. Two weeks after delivery of the drug the pharmacist sent the prescribing

Figure 1
Organogram of the flow of information



general practitioner (GP) a questionnaire. In addition, he or she sent the Netherlands Pharmacovigilance Centre Lareb, the Dutch spontaneous reporting centre, an anonymous overview of the medication history of the patient involved. Together with the questionnaire the GP received written instructions and was requested to forward the completed form to Lareb. The information flow between the three parties is depicted in Figure 1.
The pharmacists were all participants in a project analysing pharmacy data conducted by the department of Social Pharmacy and Pharmacoepidemiology of the Groningen University in the Netherlands. The pharmacies' computer systems automatically generated the signal indicating a first delivery.
This pilot study exclusively monitored prescriptions written out by GPs. The questionnaires the GPs received were perforated allowing the details of the patients to be removed before the form was submitted to Lareb. The form the GPs were asked to return consisted of a slightly moderated version of the standardised form in use at Lareb in that it did not include the medication history since this information was already provided by the participating pharmacists. The questionnaire was marked with the same code as the medication history. To guarantee that the researchers were blind to the identity of the GPs, the return envelopes were opened by secretarial staff that provided the form with a separate code.
The pharmacists and GPs made use of standard return envelopes, which ensured that at Lareb the forms submitted were processed according to the usual procedure for reports on ADRs.
Since with this pilot study we intended to test a potential method for intensive monitoring and not the drug, the choice of drug was of minor importance. We opted for rofecoxib, which drug had been released on the Dutch market six months prior to the trial. It was deemed suitable for this trial because it was a new drug that was being prescribed regularly, also by GPs. At the time of the study rofecoxib was solely indicated for symptomatic treatment of arthrosis.
After conclusion of the trial Lareb requested the participating pharmacists and GPs to fill in an evaluation form.

4.1.3 Results

In total Lareb received 44 medication histories from the eight pharmacies (seven pharmacists) participating in the trial. The GPs returned a total of 31 report forms, which implies that 70.5% of the forms the pharmacists forwarded to the GPs were submitted to Lareb. All the forms had been completed legibly and in full. On inquiry it appeared that in three instances in which the GP had prescribed rofecoxib for the first time, the pharmacist had not included the case in the trial. One case was not included because the prescriber and patient were one and the same person and

in the two other cases the pharmacist involved had mistakenly omitted inclusion.
In 19 of the 31 submitted reports the GP had seen the patient again and in 2 cases an adverse event was reported, both relating to gastric complaints. In one case the patient involved had been prescribed rofecoxib before.
Since we were interested in finding out whether it was possible to speed up the data collection process of newly marketed drugs, we compared the date the selected drug was prescribed with the date the report forms were received by Lareb. With the exception of one report all forms had been submitted within six weeks after the drug had been dispensed.
Although outside the scope of this trial, the medication histories and report forms Lareb received did provide some insight into the prescription behaviour and use of rofecoxib (e.g. the patients' age and gender and dose prescribed) in the clinical practice. From the 44 medication histories it was derived that, apart form one case, the recommended initial dose for elderly patients (12,5 mg) was not adhered to and a dose of 25 mg had been prescribed in 43 cases. The 31 forms returned by the GPs, however, showed that 16 of the 31 patients had been above the age of 60. This discrepancy might be explained by the fact that health insurance companies in the Netherlands only provide full coverage for a 25-mg dose. Moreover, in the case of a first delivery, compensation is restricted to a maximum of 15 days, which held for 37 of the 44 prescriptions. Eleven of the 31 forms stated arthrosis as the indication.
All participating pharmacists completed the evaluation form. The most frequent remarks made concerned practical matters such as the return envelopes – the two separate envelopes for the prescribing GP and Lareb – which were too much alike. In all cases pharmacists and GPs had been in contact to discuss the trial. Two pharmacists had reservations about cooperating in the proposed method of Intensive Monitoring on a long-term basis. For one pharmacist this was due to practical reasons (discontinuation of his association with the pharmacy), and the second pharmacist indicated not to be able to provide an unequivocal response. Two pharmacists expressed their doubts as to whether GPs would be prepared to make a long-term commitment to the proposed system.
The GPs were requested to return their evaluation forms via their pharmacist to prevent their identity from becoming known to the researchers. In total Lareb received seven completed forms. A remarkable finding was that three of these originated from GPs who had not reported adverse drug events to the national reporting centre Lareb before. Six GPs recognised the potential of the proposed drug monitoring system. One GP had reservations and mentioned time required for the method and lack of financial compensation as prohibitive.

4.1.4 Discussion

Cooperation of pharmacists and physicians

The main outcome of this pilot study is that a system of Intensive Monitoring is feasible, allowing information about the effects of newly released drugs in daily practice to become available at an early stage. Pharmacists and GPs are willing and have the capability to cooperate in such a system. The pharmacist has a pivotal role in the proposed system, both with respect to signalling a drug's first delivery and submission of the medication history to the national spontaneous reporting system, as well as forwarding the report questionnaire to the prescribing GP. The eight pharmacies participating in this trial used three different computer systems. All three systems proved to have the facility to generate a first delivery signal. In one instance only, this function could be linked to an electronic agenda, which could automatically generate a reminder indicating the date for the GP forms to be sent out. Although the number of participants in this pilot study was limited, it can be concluded that the contribution and cooperation of the GPs and pharmacists was quite satisfactory. It needs to be noted that the pharmacists involved were all experienced in participating in scientific research. An earlier study found that, overall, pharmacists in the Netherlands are motivated to play an active role in pharmacovigilance.(12)

If the number of pharmacists and clinicians were to be extended, apart from early detection of adverse drug reactions, the system would also lend itself for more elaborate research on drug-related aspects. Thus, insight may be gained regarding the market penetration of a new drug, the indication for which it is prescribed and user characteristics such as age and gender. In addition, because the system provides data on both the user population and the use of the drug, Intensive Monitoring is, in principle, also suitable for quantitative analyses.

This pilot study investigated the use of the system in primary health care. It is also feasible for dispensing pharmacists to generate first deliveries prescribed by specialists in a similar fashion. Patients that have been admitted to hospital get their medication from the hospital's in-house pharmacy. The response is likely to be lower since it is known that, compared to GPs, medical specialists are less willing to cooperate in a reporting system. (13) Examples of Intensive Monitoring in a clinical setting have been described earlier, for instance in the USA.(14)

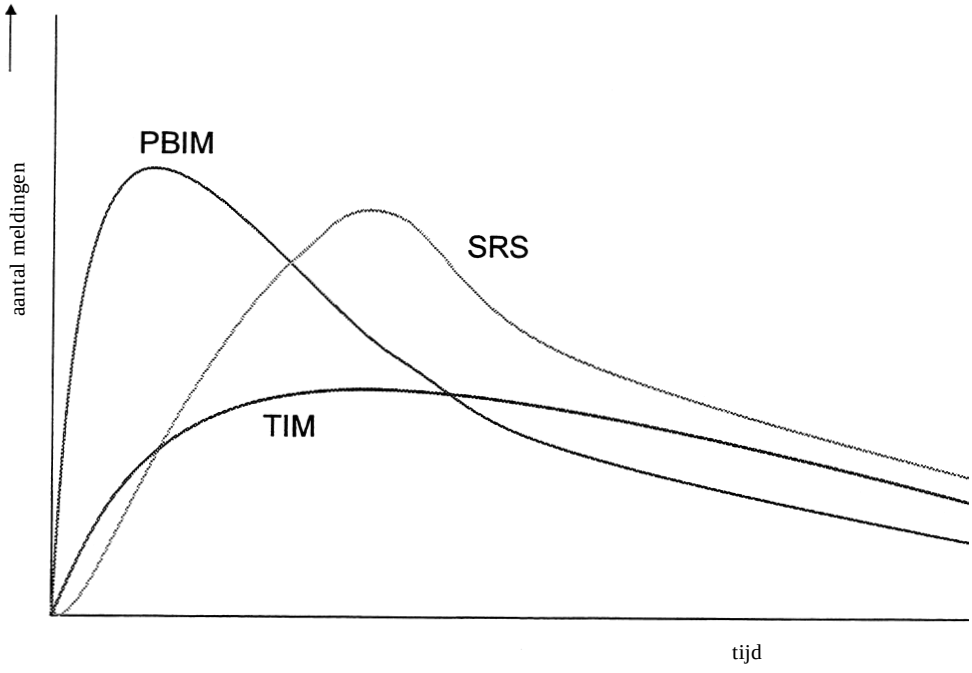
Comparison with existing Intensive Monitoring systems

The system proposed in the present study distinguishes itself from the methods of Intensive Monitoring operative in New Zealand and the United Kingdom with respect to several aspects.

Firstly, the system we tested makes information about a newly introduced drug

Figure 2

Schematic curves of number of reports in relation to time for different ADR reporting systems



PBIM: Pharmacy-based Intensive Monitoring
TIM: Traditional Intensive Monitoring
SPR: Spontaneous Reporting Systems

available more quickly. Figure 2 shows schematic the different curves of number of reports related to time. All three systems have a period of time between the introduction of a drug and the decision to start the Intensive Monitoring. When this decision is made, in our system there is only a short time needed to inform pharmacists to provide the first delivery signal and to send the reporting form to the prescribing physician. The existing systems need more time to get the wanted information. Of course there need to be a sufficient number of prescription of the drug under investigation in order to get enough reports, however in our opinion the quality of the reports adds more the outcome of reporting systems as the number of reports does.(15)

Secondly, the method with which the data are collected is considerably less complicated and more cost-effective than its counterparts in New Zealand and the

UK since the proposed reporting system closely resembles the reporting methods pharmacists and GPs are already familiar with. There is no need for a separate administrative system to collect the prescriptions and to receive the wanted information from the prescribing physician.
The burden on the pharmacist is higher than in the two existing systems and less taxing for the GP because a number of details can be derived from the medication history that is provided by the pharmacist. However, this additional task it not likely to be prohibitive since pharmacists in the Netherlands generally already regard reporting as an integral part of their task in providing pharmaceutical care.
In terms of efficiency, the national pharmacovigilance centre has much to gain from this system. The spontaneous reporting system receives these reports much like other reports and can include them in the standard processing procedure by simply labelling the reports as originating from Intensive Monitoring. There is one drawback in that all first deliveries need to be recorded, whereas only a small percentage will lead to the GP reporting an adverse reaction. This implies that the capacity of the reporting system will possibly need to be expanded, although an automated data exchange will keep this to a minimum.
A noteworthy detail in this context is that Intensive Monitoring has predominantly received the attention of pharmacovigilance centres that work independently from the approval authorities. This applies to both New Zealand and the United Kingdom as well as to the Netherlands Pharmacovigilance Centre Lareb.

Possible future developments
Large-scale application of the presented system appears possible. The Netherlands has 1200 pharmacies and with ten first deliveries of a drug under investigation the burden will be limited while at the same time data about well over 10,000 deliveries can be obtained. Nevertheless, a comprehensive implementation of such a system will have its limitations.
Whereas pharmacists appear to be motivated to contribute to Intensive Monitoring, whether this will also hold for GPs and other clinicians when the system is applied on a national scale is uncertain. In general, the existing spontaneous reporting systems depend on a select, motivated group of physicians; many practising clinicians do not contribute to the system.(11) Our trial was restricted to GPs and earlier experiences in research involving medical specialists did not look promising. Their reluctance to participate may lie in the fact that a monitoring system requires their personal cooperation whereas in the case of pharmacists use can be made of the pharmacy's computer system and infrastructure.
Further development of the proposed method and integration of the computer systems of pharmacies and GP surgeries – steps towards which are currently being undertaken in the Netherlands – will facilitate the electronic exchange and

processing of the various data thereby considerably reducing the burden to pharmacists and doctors as well as the national reporting system. In this way the GP merely needs to report the suspected adverse event and the subsequent additional information required will be automatically provided, matched and transferred.

Additional remarks

Post Marketing Surveillance is especially needed to detect type B adverse drug reactions and in a lesser extend type A reactions.(16) Type B reactions have a suggestive time relationship, but will not always be detected in the few weeks between the prescription and the moment the prescribing physician fill in the reporting form. In the present trial the prescribing physicians were only asked to fill in a form once, which they returned to Lareb within four weeks. This speed is essential for a system aimed at a prompt detection of signals of as yet unknown adverse drug reactions. The system may be extended by sending out a second form after for instance three months, thus allowing information about drug reactions to be gathered in the longer term.

In our system the pharmacovigilance centre receives all the information needed, also the concomitant medication. This gives also the possibility to detect interactions.

An important positive side effect of implementation of the proposed system deserves special mention. Application of the method will actively involve doctors and pharmacists in the much-needed process of pharmacovigilance. Of the seven GPs who submitted their evaluation to Lareb three had not reported an adverse reaction before. In other countries findings also indicate that Intensive Monitoring may induce spontaneous reporting of suspected adverse reactions to drugs.

4.1.5 Conclusion

It is vital that after introduction of a drug information about possible associated adverse effects can be obtained as soon as possible. The existing monitoring methods are not designed for this purpose. The method for Intensive Monitoring proposed in this article, which makes use of the first delivery signals from pharmacists, was designed to fill this gap and a first, tentative trial found it to be a fast and efficient approach. Both pharmacists and GPs willingly cooperated and proved to be able to contribute actively in this new system facilitating the intensive monitoring of new drugs.

Acknowledgement

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Chapter 4.2

Do pharmacists' reports of adverse drug reactions reflect patients' concerns?

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Abstract

Aim of the study

The aim of the present study was to investigate whether the concerns patients express to a Drug Information Line about possible adverse drug reactions (ADRs) they have experienced, are sufficiently reflected by the ADR reports submitted by pharmacists to the Netherlands Pharmacovigilance Centre Lareb with regard to the type of ADRs and the drug groups involved.

Methods

ADR-related questions patients addressed to the Dutch Drugs Information Line were compared with the ADR reports pharmacists sent in to Lareb in the same period. The similarities and differences between the two datasets as the characteristics of the suspected ADRs and the kinds of drugs mentioned were investigated, as well as the severity of the reported ADRs. To compare the two data sets and to establish whether significant differences were present, a logistic regression analysis was conducted on the reported drugs and ADRs.

Results

Analysis of the content of the phone calls yielded 1168 (14.6%) calls concerning possible experienced ADRs. The suspected ADRs pharmacists reported to the Netherlands Pharmacovigilance Centre Lareb in the same period included 1,734 reports. There were only slight differences between the queries patients put to the Drug Information Line regarding possible adverse drug reactions and the reports on suspected ADRs pharmacists submitted to the pharmacovigilance centre. With respect to possible ADRs in the psychiatric spectrum and ADRs associated with the use of antidepressants, there seems to be a deficiency in the reporting by pharmacists.

Conclusion

The ADRs pharmacists report to the national pharmacovigilance centre reflect patients' concerns about ADRs they experience in relation to the medication they are taking.

4.2.1 Introduction

Patients are sometimes concerned about the drugs they take and prove to have a great number of questions about these drugs.(1) It goes without saying that they can address these questions to the prescribing doctor or the dispensing pharmacist to have them look into their queries. However, patients in the Netherlands have also the opportunity to put their questions regarding medication to the national Drugs Information Line (DIL), an initiative of the Royal Dutch Association for the Advancement of Pharmacy (KNMP).(2) This information line is open during office hours; 150 pharmacists provide this service on a voluntary basis. A summary of each telephone conversation is stored in a database. The DIL first became operational in 1990 and at present approximately 10,000 questions are dealt with.

The Netherlands Pharmacovigilance Centre Lareb is the national centre to which doctors and pharmacist's report suspected adverse drug reactions (ADRs).(3) A substantial part (40%) of the number of reports Lareb receives is submitted by pharmacists.(4) This is not surprising since the Dutch pharmacists have made the monitoring of the use of medication and pharmacovigilance one of their priorities in the context of the pharmaceutical care they provide.(5-7)

In recent years there has been an ongoing debate about the potential contribution direct consumer reporting of possible ADRs might have for pharmacovigilance.(7,8) One of the arguments in supporting patient's reporting system is that reporting by patients could help solve the current underreporting of ADRs. Other considerations that have been mentioned concern claims that through consumer reports adverse events may possibly be detected earlier or that adverse reactions may be brought forward that might otherwise escape the attention of health professionals.(9,10)

Observations and reports made by health professionals generally are a combination of an interpretation of a description originally provided by the patient and objective information.(11)

In an earlier study regarding the Drug Information Line, Van der Toom and colleagues studied the question to the DIL during three short periods.(12) Egberts and colleagues compared information derived from the DIL database with data from physicians and pharmacists in the Lareb database and evaluated patient characteristics and the drugs involved.(13)

In the present study we compared the ADR-related questions patients put to the Drugs Information Line with the ADR reports pharmacists sent in to Lareb in the same period. More specifically, similarities and differences between the characteristics of the suspected ADRs and the kinds of drugs mentioned were investigated. The aim of the study is to establish whether the reports of pharmacists adequately reflect the questions patients have in relation to possible ADRs they have experienced themselves.

4.2.2 Methods

In our study we compare two datasets: one of questions to the Drugs Information Line and one of pharmacist's reports to the Netherlands Pharmacovigilance Centre Lareb regarding drugs and ADRs. The study covered the period between 1 January 1998 and 15 March 1999 and, given that both the Drugs Information Line and Lareb work on a national scale, entailed a nationwide comparison. The entire range of questions the DIL processed during this period was analysed and coded by an experienced assessor. The questions related to possible experienced adverse events were selected and subsequently categorised for further analysis. Only those questions with the following criteria were included in the analyses: the suspected drug could be identified, the adverse drug reaction had been experienced by the caller him/herself and the caller's sex was known. Enquiries about possible ADRs and calls with too general complaints were excluded.

The ADRs mentioned by the various patients were assigned a so-called WHO preferred term. Subsequently, each preferred term was assigned to one System Organ Class (SOC), i.e. a group of preferred terms pertaining to the same organ system.(14) The drug concerned was coded according to the first position of the Anatomical Therapeutical Chemical system (ATC-system).(15)

Similarly, all the reports of suspected ADRs Lareb received from pharmacists during the period under investigation were selected and subsequently coded using the procedure described above.

To compare the two data sets and to establish whether significant differences were present, a logistic regression analysis was conducted on the reported SOCs and ATC codes. The odds ratios, (ORs) adjusted for age and gender, of the various SOCs and ATCs as reported by patients (DIL) and pharmacists (Lareb) were

Table 1

Number of questions (DIL) and reports (Lareb), ADR-related questions and reports, included cases, suspected drugs and reported adverse drug reactions from the Drug Information Line and from the pharmacist reports submitted to Lareb (1/1/98 – 15/3/99)

	DIL	Lareb
Total number of questions DIL and pharmacists reports to Lareb	8340	1734
Number of questionsabout experienced ADRs	1168	1734
Number of included cases	1041	1734
Number of suspected drugs	1041	1814
Number of reported adverse drug reactions	1323	2426

calculated as well as the corresponding 95%-confidence intervals. For the statistical analysis SPSS 10.0 was used.
Next, for both groups the proportion of possible serious reports was estimated. For this procedure we applied the criteria for 'critical term' as defined by the WHO.(16) Critical terms are a subset of the WHO preferred terms indicative of serious disease states that warrant follow up. For this reason critical terms may be of particular interest for signal generation.

4.2.3 Results

In the study period the suspected ADRs pharmacists reported to the Netherlands Pharmacovigilance Centre Lareb that were included in our study totalled 1734 reports, of which 595 concerned men (34.3%) and 1139 women (65.7%). In the same period the DIL processed 8012 queries by patients. Analysis of the content of the calls yielded 1168 (14.0%) calls concerning possible or suspected ADRs experienced by the caller themselves. In total, 1041 of the 1168 cases (12.5% of the total number of calls) could be included because ADR, suspected drug and sex of the patient were known. Of these cases, 299 involved men (28.7%) and 742 women (71.3%). The number of included

Table 2

Distribution of drugs according to ATC main group of reported ADRs of the Drug Information Line (n=1041) and pharmacists' reports to the Netherlands Pharmacovigilance Centre Lareb (n=1814).

Code	ATC main group	DIL	Lareb	Odds	95% conf. int.
A	Alimentary tract and metabolism	50	142	1.68	1.21-2.34
B	Blood and blood forming organs	33	55	0.94	0.61-1.46
C	Cardiovascular system	182	453	1.55	1.28-1.88
D	Dermatologicals	18	47	1.49	0.86-2.59
G	Genito-urinary system and sex hormones	83	118	0.83	0.62-1.11
H	Systemic hormonal preparations	42	34	0.46	0.29-0.74
J	General anti-infectives for systemic use	45	222	3.05	2.19-4.24
L	Antineoplastics and immunomodulants	15	32	1.22	0.66-2.27
M	Musculo-skeletal system	49	134	1.65	1.18-2.31
N	Central nervous system	462	339	0.29	0.24-0.34
P	Antiparasitic products	6	38	3.64	1.53-8.65
R	Respiratory system	46	138	1.77	1.26-2.50
S	Sensory organs	6	28	2.79	1.15-6.77

Only those System Organ Classes that have more than 5 cases are included in this table. The Odds is adjusted for age and gender.

suspected drugs and reported ADRs to Lareb by pharmacists and those reported from the Drug Information Line are shown in Table 1. The differentiation in the drugs involved, as reported by pharmacists (Lareb) and by patients (DIL) can be found in Table 2. The differences in the reported ADRs as coded per SOC for both groups are shown in Table 3.

Table 3

Distribution of System Organ Classes for ADRs reported by patients to the Drug Information Line (n=1223) and for ADRs reported by pharmacists to the Netherlands Pharmacovigilance Centre Lareb (n=2426).

Code int.	System Organ Class	DIL	Lareb	Odds	95% conf.
100	skin and appendages disorders	86	369	2.60	2.04-3.32
200	musculo-skeletal system disorders	53	119	1.21	0.87-1,68
410	central and peripheral nervous system d.	181	337	1.03	0.85-1.25
431	vision disorders	44	103	1.28	0.90-1.84
432	hearing and vestibular disorders	9	19	1.12	0.50-2.49
433	special senses other disorders	18	67	2.20	1.19-3.42
500	psychiatric disorders	220	230	0.50	0.42-0.63
600	gastro-intestinal system disorders	215	414	1.07	0.90-1.29
800	metabolic and nutritional disorders	44	32	0.38	0.24-0.61
900	endocrine disorders	8	11	0.69	0.28-1.74
1010	cardiovascular disorders – general	11	18	0.90	0.43-1.92
1030	heart rate and rhythm disorders	29	57	1.05	0.67-1.65
1040	vascular (extracardiac) disorders	11	28	1.39	0.69-2.80
1100	respiratory system disorders	38	131	1.92	1.33-2.78
1230	platelet, bleeding & clotting disorders	16	50	1.67	0.95-2.95
1300	urinary system disorders	9	31	1.88	0.89-3.96
1410	reproductive disorders, male	18	11	0.27	0.13-0.58
1420	reproductive disorders, female	40	54	0.80	0.54-1.21
1810	body as a whole – general disorders	243	288	0.60	0.50-0.73

Only those System Organ Classes that have more than 5 cases are included in this table.
The Odds is adjusted for age and gender.

drug categories

Looking at the drug categories, we observed that the number of reports from pharmacists to Lareb was significantly higher for medication directed at treatment of disorders in the alimentary tract and metabolism, cardiovascular system, antibiotics, musculo-skeletal system and respiratory system (Table 2). By contrast,

the DIL answered significantly more questions about hormone-based medication (excluding sex hormones) and drugs affecting the nervous system.

adverse drug reactions
The number of questions that the DIL received about adverse drug reactions was higher for the following SOCs: psychiatric disorders, male reproductive disorders and also for autonomic nervous system disorders (significant, but low numbers) – see Table 3.
The ADRs for which Lareb received a higher number of reports from pharmacists involved the following SOCs: 'Skin', 'Special Senses' and 'Respiratory System'.

severity of the suspected ADR
Regarding the severity of the suspected ADR, as expressed by the number of reports that met the criteria for 'critical term', we found that of the Lareb reports 264 out of 1223 (11.9%) met this standard and this was 91 (7.4%) for the questions posted to the DIL. Thus, the number of reports on serious ADRs was statistically significantly higher for the pharmacists report to Lareb: OR 1.58 (95% confidence interval: 1.23 – 2.02).

4.2.4 Discussion
The findings of our study show that there are only slight differences between the reports on suspected ADRs pharmacists submitted to our pharmacovigilance centre and the queries patients put to the Drug Information Line regarding possible ADRs.

The majority of the patients reported on by the pharmacists to Lareb and the callers to the DIL, was female. This should be seen in the light of the greater medical consumption by women and their concomitant higher use of medication.(17)
The need for more information about the drugs being taken and in particular details regarding possible ADRs is evident. We included only those questions that concerned possible ADRs the patients had experienced themselves that could be coded as a WHO preferred term and of which the suspected drug was known (14.0%). This explains the difference with the study by Van der Toom et al. and Egberts et al. who found that respectively 21.6 and 28% of the callers' queries concerned adverse events.(12,13)
Although the difference between the ADRs pharmacists reported to Lareb and the complaints the DIL received was significant for the SOCs autonomic nervous system disorders and male reproductive disorders, the numbers involved were small. This also applies to the SOC metabolic and nutritional disorders mainly associated with obesity. For both these categories of questions holds that the caller seems to appreciate the anonymity of the DIL.

Many callers mentioned possible ADRs related to psychiatric disorders. This is not exceptional since a considerable proportion of the reports Lareb receives also falls into this category. Apparently, questions relating to these subjects are not as easily put to the pharmacist, which prevents patients from reporting any such adverse effects. Patients rather turn to their doctor or, again, prefer to call an anonymous helpdesk. It needs to be noted that an earlier study had revealed that with respect to the SOCs male reproductive disorders and psychiatric disorders Lareb received significantly more reports from medical practitioners than from pharmacists.(13,17)
As regards to the drugs for which adverse reactions were reported, we found that, compared to the pharmacist reports, the number of calls to the DIL about drugs affecting the CNS were far higher. The calls mainly concerned the largest type of drugs of this category, i.e. antidepressants. Van der Toom et al. found also CNS drugs as the biggest group and Egberts et al. had earlier reported a similar finding regarding antidepressants.(12,13)
This is not surprising since the use of antidepressant drugs is still increasing. The proportion of both adverse events of a psychiatric nature and events associated with the use of antidepressants is higher for the DIL when compared to the number of these ADRs in the pharmacists' reports to Lareb. Despite the fact that pharmacists also operate the DIL, as mentioned earlier the anonymity of the helpline seems to play a role. The professional background of the person answering the call does not appear to play a role in the patient's decision to call the DIL. It is possible that for concerns that relate to the patient's private life, patients are more inclined to turn to the DIL and since it is exactly this type of query that worries most users, the need for a second opinion may be high. This fact may also explain the high incidence of calls of this nature.
With respect to the severity of the ADRs reported we found that the proportion of pharmacist' reports signalling a possibly serious ADR was higher than the number of questions about possible serious adverse drug reactions addressed to the helpline. This seems to imply that for serious complaints patients tend to go straight to a pharmacist.
In general, pharmacists' reports to the Netherlands Pharmacovigilance Centre Lareb prove to be a good reflection of the questions patients have regarding ADRs. Pharmacists consider answering questions from patients' part of the pharmaceutical care they give, which function has been fully integrated in the pharmacies' operational procedures. This should be considered in the discussion about the value of direct ADR reporting by patients, however other and more specific reporting facilities for patients to report possible ADRs should be taken into account in this discussion.(8)
The organisation of a helpline is quite complex: a considerable number of volunteer pharmacists and organisational adaptations are required to operate such a system.

These pharmacists have also the possibility to report a possible ADR to the national pharmacovigilance centre, which is seldom done for questions answered through the Drug Information Line.
This study has some weaknesses. It should be taken into account that no causality assessment has been performed. Such an assessment was not possible due to the limited information that is obtained from callers to the DIL. This prevents conclusions to be drawn about possible new signals of an ADR. It may be possible that some questions to the DIL, if reported to their pharmacist, will be sorted out because they were not considered to be a possible ADR in his of her professional view. Reports from pharmacists to the national pharmacovigilance centre are far more detailed in comparison with the information given to the information line.
This study should not be regarded as a comprehensive study. Of the two groups investigated, only a limited number of factors have been compared. The Drug Information Line is not designed for the detection of ADRs and only limited information is available. Moreover, possible ADRs are not recorded in a standardised way. It also needs to be noted that it was not possible to determine how many of the questions patients put to the Drug Information Line had also been put to their health professionals, who subsequently reported these to Lareb.
Both groups which we compared in this study involved pharmacists. The Drug Information Line is staffed by pharmacists and only the reports pharmacists submitted to Lareb were taken into account. Despite the fact that pharmacists are quite willing to answer patient questions about drug use and problems in their pharmacies, for some users the threshold seems too high. These individuals prefer to call the DIL. This finding indicates that the role of the pharmacist, being an expert in his/her field and thus best equipped to provide independent, professional information in the pharmacy, should be enforced. It is also recommended that the patient leaflet inform drug users about the fact that possible adverse drug reactions should be notified to their health professional, physician or pharmacist.

4.2.5 Conclusion

Patients take a keen interest in the drugs they are taking and are frequently in search of answers to questions concerning these drugs. A substantial part of their worries concern possible ADRs. Although the prescribing doctor and dispensing pharmacist are the most obvious and best-equipped persons to address these questions to, a telephone service providing information on drugs appears to fulfil a need. A comparison of the reports pharmacists submit to a spontaneous reporting system with questions put to a drug information line shows that, for the aspects investigated, the nature of ADRs as reported by pharmacists match the features of the phone queries. However, particularly with respect to possible ADRs in the psychiatric spectrum and suspected ADRs associated with the use of

antidepressants, there proves to be a deficiency in the reporting by pharmacists, but are within Lareb corrected by a higher proportion of reports from physicians. Despite this obvious limitation, it may be concluded that, in general, the ADRs pharmacists report to the national pharmacovigilance centre adequately reflect the patients' concerns about possible ADRs associated with the medication they are taking.

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Chapter 4.3

Consumer reporting: a new step in pharmacovigilance? - An overview.

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Abstract

The direct reporting of adverse drug reactions by patients is becoming an increasingly important topic for discussion in the world of pharmacovigilance. At this time, few countries accept consumer reports.
An overview is given of experiences with consumer reporting in various countries of the world. The potential contribution of patients reports of adverse drug reactions is discussed, both the qualitative and quantitative contribution. The crucial question is one of whether patient reports will increase the number and quality of the reports submitted and/or lead to a more timely detection of signals of possible adverse reactions, thus contributing to an enhancement of the existing methods of drug safety monitoring. To date, the data available are insufficient to establish such added value.

4.3.1 Introduction

The direct reporting of adverse drug reactions by patients is becoming a increasingly important topic for discussion in the world of pharmacovigilance. In several countries there is an ongoing debate about the question or consumer reports without physicians or pharmacists as a intermediate are desirable. In this paper we use the term consumer reporting, however it might be argued that the word consumer relate more to a commercial product as to a health care product. Patient reporting could be a better term, relating it more to patients than to the producer's side of drugs.(1)

A key problem in the discussion about the usefulness of consumer reporting is the fact that there is little evidence, especially when we relate consumer reporting to spontaneous reporting. All the information available in the literature regards research using questionnaires or using a drug information service, and is not the results of experiences with consumer reporting to a centre that collects spontaneous reports.(2-7)

In this overview we will make an inventory of experiences with consumer reporting in various countries of the world. The potential contribution of patients reports of adverse drug reactions will be discussed, both in terms of their qualitative and quantitative contribution.

4.3.2 The necessity of pharmacovigilance

The advent of pharmacotherapy based on recent scientific advances in the first half of the twentieth century brought about revolutionary changes in the scope of cures for numerous diseases. These innovations were of course enthusiastically welcomed, and this welcome was almost without question; the negative aspects of pharmacotherapy received little or no attention. Only when adverse reactions of a particular drug were evident, were critical questions asked, but otherwise scrutiny was never systematic.(8)

It was the Dutchman Meyler who, in 1951, was the first to provide a systematic overview of 'side effects of drugs'. His work formed the basis of what is, on an international scale, still regarded as the standard work in the field of adverse effects of drugs.(9)

The thalidomide tragedy in the early 1960s induced many countries to set up national bodies to monitor the safety of drugs, also known as pharmacovigilance centres. The underlying motive for the establishment of such national centres was that, by giving physicians and pharmacists the opportunity to report suspected adverse events, potential but as yet unknown side effects of drugs would be detected at an earlier stage. It was thought that serious and extensive damage as had been caused by thalidomide could thus be prevented. European legislation has led to uniformity in pharmacovigilance within the European Union by stipulating

which tasks and responsibilities are to be carried out and assumed by the national governments, the pharmaceutical industry and the various professional groups involved.
Many countries, among which all EU member states, have organised their reporting systems for potential adverse events in such a way that only physicians and pharmacists are qualified to report.(10) In a number of countries pharmacists are not necessarily authorised to report.(11)
This method of collecting and analysing data from the health care sector is called a 'spontaneous reporting system' (SRS), the word spontaneous in this context meaning that reporting is not compulsory. Consumer reporting was never before an item in the organisation of SRS; it is only recently that consumer has become a point of discussion. When we use the term consumer reporting, it is about users of drugs reporting suspected adverse drug reactions to a spontaneous reporting system.

4.3.3 International experiences and developments concerning patient reports

To date there is little practical experience with patients reporting adverse drug reactions. In a limited number of countries the national reporting system provides some (formal) room for patient reports. Below we will discuss the current situation on consumer reporting in various countries.

United States

MedWatch, the FDA's Safety Information and Adverse Event Reporting Program, offers patients some scope to directly report adverse drug reactions. The majority of reports originating from patients that actually reach the FDA, however, are sent in by the pharmaceutical industry. This sector has the legal obligation to pass on all reports it receives. Thus, questions and complaints from patients concerning drugs addressed to the marketing authorisation holder are categorised as patient reports. A mere 12% of all reports the FDA receives have been directly submitted by physicians, pharmacists or health consumers. Approximately a third of these reports stem from patients.(12) No publications have been done yet about the contribution of consumer reports to the FDA.

Australia

Since the early 1990s Australia has been taking its first steps towards creating facilities allowing patients to report complaints on drugs. The Australian Patient Safety Foundation runs and maintains the Australian Incident Monitoring System (AIMS). However, only 20% of the reports concern medication and only 4% of these are about adverse events. The national reporting system (ADRAC) receives about 10,000 reports per year and this includes all appropriately documented patient reports. On an annual basis the latter comprise fewer than 100 reports.(13)

Scandinavian countries

In September 2000 Kilen, the Swedish Consumer Institute for Medicines and Health, organised a conference that was announced as the 'First International Conference on Consumer Reports on Medicines'.(14) The key topic of the conference was: Should patients be given the opportunity to report possible adverse drug reactions direct to a national body? Kilen does collect patient complaints about drugs in Sweden and Norway although these complaints specifically concern addiction to benzodiazepines and lorazepam in particular. Thus, practical experience with comprehensive consumer reporting is still limited and Kilen's full objectives have as yet not been implemented. Remarkable is the fact that in the Scandinavian countries pharmacists are not allowed to report ADRs to their national centres.

The Netherlands

In the Netherlands there is no hands-on experience with consumer reporting although some research into the topic has been conducted. In 1998 the Wetenschapswinkel Geneesmiddelen (Science Shop for Drugs) of the Faculty of Pharmacy of the University of Utrecht published a study in which it was investigated which specific facilities would allow patients to report side effects in the Netherlands and how these facilities could be adjusted and extended.(15) In a round-table conference following the project it was concluded that further research into consumer reporting was desirable. Also, two Dutch hospitals have conducted research into patients as information source for possible adverse events.(2)

Recently the Dutch Consumer Association insisted on the fact the consumer should be able to report suspected adverse drug reactions to the national pharmacovigilance centre.

United Kingdom

In the UK the Consumers' Association has also suggested that patients should perhaps be offered facilities to report on adverse drug reactions.(16) Again, as in Sweden, the late discovery of dependency on benzodiazepines was mentioned as an example of signals that might be reported earlier by patients than professionals.

The Medicines Control Agency (MCA) maintaining the national reporting system in the UK has responded with caution based on both intrinsic and practical arguments. Nevertheless, in the UK the National Health Service does facilitate the reporting of complaints by patients, and, although the emphasis is not on drugs, adverse effects are also mentioned in this context.(17) Recently there are new developments regarding direct consumer reporting because of the intended merger of the Medicines Control Agency and the Medical Devices Agency. The Medical Devices Agency accepts patients reports and once the agencies emerge it is would be possible the new agency also accept direct reports from consumers of pharmaceuticals.(18)

The Internet

Novel is the emergence of web sites on the Internet offering patients a forum to exchange their experiences with drugs. Apart from being an expression of the patients' need to share and exchange information about medication, the phenomenon also shows that patients are a rich source of information. It is evident, however, that distinguishing valuable from unreliable data on the Internet poses a real problem.(19)

4.3.4 Potential contribution of patient reports on adverse reactions

In the debate on the advisability of offering patients facilities to report suspected side effects of drugs, various issues play a part. These will be outlined next.

Qualitative contribution

It is to be expected that reports from a patient perspective will cause a shift in the type of adverse reactions being reported since the reports that now reach the reporting systems may not reflect the adverse events that were originally reported because of the filter applied by physicians and pharmacists.(7) With patient reports, not only side effects that health professionals generally consider less relevant will receive attention, but also complaints that are usually less easily communicated, for instance those relating to sexual matters.(20) Similarly, adverse effects caused by the off-label use of medication (applications deviating from the approved indication) are probably less likely to be reported by doctors than by patients. In addition, doctors may not always be familiar with certain over-the-counter drugs or alternative medication.

Quantitative contribution

Consumer reporting will raise the number of reports submitted, which will enhance the impact of the reporting systems. Despite the fact that research has repeatedly shown that in the Netherlands the basis of trust between patients and their doctors and pharmacists is such that this generally does not form a major obstacle, the fact that less than 10% of the professionals involved effectively pass on reports does put things in an different perspective: many complaints from patients appear to founder on the reluctance of the health care professionals.(21) The huge number of queries the Dutch Geneesmiddelen Info Lijn (Drug Information Line) receives suggests that the number of reports submitted by patients may be considerable.

Political and strategic considerations

An important consideration in support of direct reporting by patients is the fact that, given today's increasing patient awareness and emancipation, it is desirable that patients are given the opportunity to report suspected side effects themselves.

After all, it is the patient that experiences the adverse reactions, which makes him or her the hands-on expert.
Reporting through GP or pharmacist implies that complaints are filtered out, which prevents patient complaints from reaching the reporting system. Since patients and consumer organisations have acquired a considerable say in determining health care policy, perhaps this argument may carry more weight than before.

4.3.5 Possible objections to and limitations of patient reports

Consumer reporting does not seem to get off the ground properly anywhere. Apparently, there are serious obstacles that prevent a timely establishment of reporting systems for the collection and evaluation of adverse drug reactions reported by patients.

Establishing the contribution of patient reports in relation to the existing signal detection systems

The main obstacle for the development of consumer reporting systems is the fundamental question regarding their intrinsic value.
The existing reporting systems, primarily based on spontaneous reporting by doctors and pharmacists and on obligatory reporting by marketing authorisation holders, have evolved extensively over the past few decades, particularly with respect to both the quality and the analyses of the reports.
As far as we know, no research has been conducted to show that extending the current systems to include reports from patients will add to their value when the size and speed of signal generation and detection are concerned.

Quality of patient reports

A key issue concerns the quality of the reports submitted by patients. Firstly, the quality as regards the selection of the reports is at stake: Are patients capable of distinguishing possible adverse drug reactions from other complaints associated with the use of medication? A second aspect relating to the quality of patient reports is their documentation. Is a lay reporter capable of providing a clear and objective description of the side effects and can he or she supply the relevant clinical information necessary for an adequate evaluation of the report?

4.3.6 Discussion

Since during the clinical trials, carried out in the evaluation and marketing authorisation stages, the safety of drugs can only be investigated to a limited extent, it is essential to also monitor their safety after marketing. For this purpose, many countries have set up a national pharmacovigilance system, which, as a rule, functions on the basis of spontaneous reporting by physicians and pharmacists. In

this paper the advisability of direct reporting of potential adverse drug reactions by patients was evaluated.
It is evident that patient reports are desirable from a politico-strategic perspective. Edwards has typified the reporting of side effects as concern reporting.(22) Apart from the medical professionals, the users of drugs also have such concerns. Physicians, pharmacists and patients all have reason for concern when the safety of drugs is concerned and all parties need to be able to express their worries in such a way that they can be assured that they are taken seriously and that the necessary steps will be taken. The fact that patient and consumer organisations have considerable influence on health care policy, lends validity to this argument. Consumer reporting is in line with the striving for quality in the health care system, in the evaluation of which the care taker takes up a key position. Unfortunately, to date few studies into the potential contribution of patient reports on possible adverse drug reactions are available in the literature. Both Solovitz et al. and Mitchell et al. have reported that users of drugs are capable of discriminating between side effects and other complaints or symptoms.(4,5) Mitchell et al. are more hesitant in this respect, particularly in connection with the patient's ability to associate suspected adverse events with a particular drug. However, one may ask whether this should be the reporter's responsibility. In a retrospective study Egberts et al. compared the questions posed by the users of drugs with adverse reactions reported by physicians and pharmacists in the same period.(6) It appeared that about a certain number of signals derived from the database of the official reporting system users had earlier demanded information. Van de Bemt et al. have shown that when specifically asked for them, hospital patients were able to report on side effects.(2) In this case the reported effects mainly concerned less serious reactions that were not known at the time. It needs to be noted, however, that it was not investigated whether the reported adverse reactions were effectively related to the drugs used. Jarernsiripornkul et al. reported that patients are willing to report if they are asked to do so.(3)

Both the Netherlands and Australia have been considering whether specific patient groups could function as reporting parties. Such a reporting system could be efficiently organised and could specifically analyse patients' experiences with particular groups of drugs. In this context research into new drugs aimed at particular patient groups, e.g. rheumatics or diabetics, could be thought of, during which study patient organisations could also be involved. However, if reports are expressly invited, this would be a case of Intensive Monitoring, which implies research rather than continuous surveillance.
Establishing a system to collect patient reports is no easy matter. For instance, are patients interested in a system specifically aimed at gathering suspected adverse drug reactions or would they prefer a system with a wider scope covering other

aspects of pharmacotherapy It is clear that a more comprehensive system will be quite different from a system that focuses solely on possible side effects. Either way, the evaluation and scientific analysis of the reports received will require manpower and funds. A reporting system raises expectations with those who report, i.e. they expect their reports to lead to results, and, in addition, they wish to be informed about the steps to be taken. With reporting systems for the medical professions such feedback has proved essential for their success (22).
Setting up a patient reporting system requires a separate organisation. The existing doctor-pharmacist systems are hesitant in taking on this extra task. This hesitation originates from the fear that the system will receive too much 'noise' without the added value of the new system having been established, receiving many but poorly documented reports. Again, this relates to the question whether patient reporting systems should merely concentrate on side effects or whether they should also take other aspects of drug use relevant to patients, such as queries regarding delivery and use, into account.
Reporting of experienced adverse drug reactions through a health professional could mean a kind of filtering. Also could be argued that this filter is a wished one, preventing an overload of national pharmacovigilance centre with invalid reports. There is some parallel with the discussion about direct-to-consumer drug advertisements.(23) On one hand these advertisement could stimulate consumer reporting. On the other hand in this discussion is also the question for the need of a 'learned intermediary'.(24)

Apart from reports that are submitted direct to the national pharmacovigilance centres, there are also consumer reports that are sent to the pharmaceutical companies that produce the drugs concerned. As mentioned earlier, this latter practice is quite common in the United States. A recent study has investigated the way the pharmaceutical sector deals with these consumer reports (25). Most drug companies include the information derived from such reports in their databases. Moreover, they have the legal obligation to pass on any reliable information about their products to the authorities. In most cases, however, the data received are insufficient to perform a proper causality assessment.
To be able to make a well-founded judgement on the advisability of an independent reporting system for patients the pivotal question in need of an answer is whether such a system will add to the value of the existing systems. Such a study should be carried out within the context of a spontaneous reporting system.

Establishing a patient system for political and strategic reasons only, without having established its possible added value first, falls outside the scope of pharmacovigilance. Adverse drug reactions do not only concern patients, both the prescribing doctor and

the delivering pharmacist are also involved. Reporting in cooperation with the prescribing doctor and/or pharmacist seems to be preferred method of reporting, supposing these professionals do report. The crucial question is whether patient reports will increase the number and quality of signals of adverse drug reactions and/or lead to a more timely detection of them, thus contributing to an enhancement of the existing methods of drug safety monitoring. To date, the data available are insufficient to establish such added value.

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Chapter 4.4

Labelling and 'Dear Doctor' letters - Are they noncommittal?

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Abstract

Over the past few years, a number of drugs have been withdrawn for safety reasons, either by drug approval authorities, or by the manufacturer. A recent example is the withdrawal of cerivastatin in connection with rhabdomyolysis. Several other drugs have also been taken off the market as a security measure, not because the nature of the risk involved was unknown but because the risk had proved apparently uncontainable. It seems that the inclusion of a warning or contraindication in the Summary of Product Characteristics (SPC) or sending a 'Dear Doctor' letter is insufficient to ensure compliant prescription behaviour. There appears to be a discrepancy between the careful use of evidence underpinning the SPC content and formal warnings and changes to the SPC and the effect they have on the prescription and dispensing of the drugs involved. This results in undue loss or damage for both the manufacturer and the patient.

There are no easy solutions to tackle this problem; the ineffectiveness of labelling and 'Dear Doctor' letters has ramifications for the whole regulatory/industrial/ educational complex.

We discuss briefly four possible strategies for improving the current situation, emphasising on the place the prescriber has in this process.

The first strategy is education-based. Clinicians need to know about the comparative merits of the effectiveness and risk of drugs, as well as how they work pharmacologically, toxicologically, and what interactions they have with each other.

The second strategy involves improving the information available for clinicians. Frequently, physicians do not consult the SPC for verification, leaving aside whether they have taken notice of the contents of the official SPC in the first place. It is recommended to that the accessibility of SPCs is enhanced for doctors and pharmacists, drawing attention specifically to any changes. There needs to be a single body of information that covers every drug.

The third strategy involves communication. There is much to be done in this area both in terms of follow-up and understanding of health professional's behaviour and how to empower best practise.

The final strategy involves professional freedom. It goes without saying that doctors who issue off-label prescriptions may need to justify their actions. Deviating from the SPC should always be a considered decision and health professionals need to be aware of the additional responsibilities associated with such a decision. The dispensing pharmacist can play an important role in the implementation of warnings and contraindications.

4.4.1 Introduction

Withdrawing a drug from the market is a drastic measure. Over the past few years a number of drugs have been withdrawn for safety reasons, either by drug approval authorities, or by the manufacturer. A recent example is the withdrawal of cerivastatin in connection with rhabdomyolysis, occurring especially when cerivastatin is prescribed in combination with gemfibrozil. What was remarkable in this case was the fact that the Summary of Product Characteristics (SPC) did include a warning for this interaction and also that the manufacturer had alerted the health professionals in 'Dear Doctor' letters about the complication.

Several other drugs have also been taken off the market as a security measure, not because the nature of the risk involved was unknown but because the risk had proved apparently uncontainable. It seems that including a warning or contraindication in the SPC or sending a 'Dear Doctor' letter is insufficient to ensure compliant prescription behaviour.

4.4.2 Practice

A number of studies have been published on the effects of adjustments of the SPC content and 'Dear Doctor' letters in connection with the incidence of arrhythmia associated with the use of cisapride.(1,2) Notwithstanding the fact that in the US four label changes and notifications had been issued, in 3.4% of the cases the concomitant use of at least one contraindicated drug had occurred.(1) It was not until the risks of cisapride had received more extensive media attention that the co-dispensing of drugs that should not be taken together with cisapride actually decreased.(2)

In March 2000, troglitazone was recalled from the market because of life-threatening acute liver failure. The risk was known and was referred to in the SPC. In the US the manufacturer had distributed four 'Dear Doctor' letters, which included the recommendation that liver function be tested more frequently. Although subsequently the number of patients tested increased 3-fold, a mere 5% of users were tested in the recommended frequency after 3 months on the drug.(3)

Recently, research results on the indications for which rofecoxib is prescribed were published in the Netherlands.(4) Rofecoxib was originally approved in the Netherlands for the indication 'symptomatic treatment of arthrosis'. However, promotional material directed at physicians particularly emphasised 'pain relief', even though costs are officially only reimbursed for the indication (osteo)arthrosis. An evaluation of the electronic data collected from the prescribing general practitioners showed that over 80% of the prescriptions involved a different diagnosis than that of 'arthrosis', thus constituting a deviation from the indication specified in the SPC. The researchers concluded that rofecoxib is prescribed for a wider range of indications than for which it was approved.

The content of the SPC is compiled with due consideration of the evidence available, including information from the clinical trials conducted prior to marketing authorisation. The definitive text is determined by the drug approval authorities and the SPC becomes part of the registration file. 'Dear Doctor' letters are drawn up in close co-operation with the manufacturer and the drug approval authorities. This also holds for any changes in the content of the SPC, such as alterations resulting from postmarketing research that have led to new insights into the safety aspects of the drug.

4.4.3 The problem

There appears to be a discrepancy between the careful use of evidence underpinning the SPC content and formal warnings and changes to the SPC and the effect they have on the prescription and dispensing of the drugs involved, as shown by the cases mentioned above. If and when physicians and pharmacists do not adhere to the SPC and their decisions lead to an increased safety risk, the decision to withdraw a particular drug from the market may be expedited. This results in undue loss or damage for both the manufacturer and the patient.(5) It may be argued, therefore, that physicians and pharmacists should adhere to the indications, warnings and contraindications as described in the SPC. Also, any alterations in the content of the SPC should be followed up in daily practice. The same applies for the information disseminated via 'Dear Doctor' letters.

Legally, however, physicians can deviate from the indications as described in the SPC. In some cases they have no other option, as occurs for instance in paediatric practice quite often because of lack of clinical trial information on children. In addition, warnings and contraindications can be ignored. There can be sound clinical reason in this. Clinical trial and epidemiological evidence can only provide a guide as to the normal group response to a drug or other therapy. It goes without saying that doctors who issue off-label prescriptions may be need to justify their actions. Deviating from the SPC should always be a considered decision and health professionals need to be aware of the additional responsibilities associated with such a decision.

4.4.4 Possible solutions

We are aware that as we are discussing the ineffectiveness of labelling and 'Dear Doctor' letters, it has ramifications for the whole regulatory/industrial/educational complex. The complexity of this could easily hinder the necessary debate. We will briefly discuss four possible strategies. Given that clinicians must interpret evidence and not try to force patients into convenient algorithms, what can be done to prevent the SPC from being perceived as a prescriptive legal document and to be more empowering?

1. Education

Drug therapy is a complex business. New drugs become available all the time, as well as new information on old drugs. The clinician, in particular, has the role of the 'learned intermediary' to evaluate knowledge critically and to use and explain it in a given individual setting. To be a 'learned intermediary' health professionals must understand the drugs they use and it is important to acknowledge that undergraduate curricula are overloaded, and only the rudiments of clinical therapeutics can be taught. Clinicians need to know about the comparative merits in effectiveness and risk of drugs, as well as how they work pharmacologically, toxicologically, and how they interact with each other. Then the clinicians may make logical inferences for the therapy of the patients they treat.

2. Information

Frequently, physicians do not consult the SPC for verification, leaving aside whether they have taken notice of the contents of the official SPC in the first place. It is recommended that the accessibility of SPCs for doctors and pharmacists is enhanced, drawing attention specifically to any changes. All evidence-based findings, including information obtained in clinical trials performed during the pre-marketing stage (not just didactic statements), need to be made available. Greater awareness about adverse drug reactions, regarding their significance, recognition, management and prevention, needs to be established. In order to enhance the knowledge of the effects of drugs in the clinical practice it is vital that doctors and pharmacists report suspected adverse effects to their national pharmacovigilance centres. These centres need to find effective ways to disseminate the data they have collected to the various professional groups and should be involved in and contribute to the education of health professionals. In short, there needs to be a body of information for every drug that is available from a single accessible source. There are numerous publications and websites that provide useful information but they do not have regulatory approval. The Cochrane Foundation provides useful reviewed information, but does not go far enough in factoring in knowledge other than from controlled trials. As argued above, other material is essential to bridge the gap between information from an ideal therapeutic situation and the application of such knowledge in a difficult patient.

Publication in national Drug Bulletins and issuing notices on special websites should be considered. In this context the US FDA has recently published proposals regarding improvements of the SPC.(6)

Doctors must make decisions on the relative effectiveness and risks of the treatments they advise for their individual patients. There needs to be much more thought about how to support this essential function. The UK's National Institute for Clinical Excellence (NICE) can be seen as a way forward in this respect, for the

introduction of new therapies. NICE tackles the difficult issue of reconciling relative effectiveness and cost; and issues guidelines, not mandates. A recent review of its work so far was positive, although indicating that the magnitude of the tasks facing NICE is great. The main challenge was seen as providing comprehensive treatment guidelines into which context any new treatment must be fitted.(7) Similar initiatives have been developed in the US (Centers for Education and Research on Therapeutics) and The Netherlands ('Standards' of The Netherlands Society of General Practitioners).

3. Communication

Communication is a two-way loop; one must ensure that information is received, understood and acted upon correctly before a communication can be said to have been successful.

There is much to be done in the area of communication, both in terms of follow-up and understanding of health professionals' behaviour and how to empower best practise. In the Erice Report on drug safety information it is stated that 'drug safety information must serve the health of the public'.(8) The Erice Declaration also commends the idea of actively communicating uncertainty. This is a difficult issue, but in the safety area it has a good deal to recommend it because of the tentative information about many even serious adverse drug reactions.

4. Professional Freedom and Professional Responsibility

Physicians and pharmacists have enjoyed great professional freedom. Given the experiences already described, one needs to ensure that information and systems support such freedom. This requires that more attention be given to the feedback parts of the communication loop mentioned in section 3. More stringent approaches need to be set in place to find out about deviations from SPCs. Off-label prescriptions need to be documented and any adverse effects should be reported. The impact of a change in the content of an SPC or a 'Dear Doctor letter' will be greater when these conditions are fulfilled, since they will reflect rather than force clinical practice.

4.4.5 Contribution of pharmacists

The dispensing pharmacist can play an important role in the implementation of warnings and contraindications. Increasingly, pharmacists consider providing pharmaceutical care a part of their professional responsibilities.(9) As with prescription of drugs, dispensing drugs cannot be noncommittal. Pharmacies in developed countries have sophisticated computer tools that help them monitor drugs for known interactions, contraindications and other important information contained in the SPC. To be able to monitor the indication for which the drug is

being prescribed, the pharmacist needs to be informed of the physician's indications for prescribing the drug. In practice this is as yet rarely the case and many health professionals object to providing this information. Jones et al. conclude in their study that in 89% of the cases in which cisapride had been prescribed in conjunction with a contraindicated drug, both drugs had been dispensed by one and the same pharmacy.(1) Pharmacists need to be given a pivotal role in the surveillance of the safe use of drugs.

4.4.6 Conclusion

Although careful attention is being paid to the contents of SPCs and 'Dear Doctor' letters it has become clear that this is not enough. There is a gap between the determination of an SPC and daily practice. Creative, not a legalistic ways need to be found that will fill that gap to the benefit of all concerned parties: professionals, registration authorities, pharmaceutical companies and above all: the patient involved.

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